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Respiratory Medicine (2009) **103**, 1152–1158

available at www.sciencedirect.com

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journal homepage: www.elsevier.com/locate/rmed

Ascertainment of collagen vascular disease in patients presenting with interstitial lung disease

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Received 3 October 2008; accepted 16 February 2009
Available online 21 March 2009

KEYWORDS
Antinuclear antibody;
Pulmonary fibrosis;
Interstitial lung disease;
Collagen vascular disease

Summary
Introduction: Previous studies of interstitial lung disease (ILD) suggest that prognosis and therapeutic response are influenced by the presence of underlying collagen vascular disease (CVD). Yet, what proportion of patients presenting with ILD have CVD is largely unknown. We sought to determine the frequency of a new CVD diagnosis in an ILD referral population.
Materials/patients and methods: We retrospectively studied 114 consecutive patients evaluated at the Johns Hopkins Interstitial Lung Disease Clinic for the development of CVD.
Results: In this retrospective cohort, nearly one-third of the 114 patients with confirmed ILD satisfied published criteria for a CVD diagnosis. Seventeen (15%) patients were diagnosed with a new CVD as a direct consequence of their ILD evaluation. Patients with new CVD diagnosis were younger than those without new CVD diagnosis: 51.4 years (95% CI 45–58 years) and 60 years (95% CI 57–63), respectively ($p = 0.01$). Moreover, an ANA $\geq$ 1:640 ($p = 0.03$) and elevated levels of creatine phosphokinase (CPK) or aldolase ($p < 0.001$) were associated with a new CVD diagnosis.
Conclusions: Unrecognized collagen vascular disease may be more common than previously appreciated among patients referred with ILD. High titer ANA and an elevated CPK or aldolase are associated with a CVD diagnosis in this referral population.
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doi:10.1016/j.rmed.2009.02.009

Introduction

Interstitial lung disease (ILD) may occur in the context of several collagen vascular diseases (CVDs), including systemic sclerosis, Sjogren's syndrome, systemic lupus erythematosus, rheumatoid arthritis, polymyositis and dermatomyositis.[1] When present, ILD often results in substantial morbidity and mortality.[2] The association of ILD with an underlying CVD varies widely, based both on the method used to ascertain ILD (chest radiograph, computed tomography (CT), pulmonary function testing (PFT) or lung biopsy) and on the specific CVD. Prevalence estimates of ILD in patients with an established CVD are largely based on patients presenting with non-respiratory symptoms of the respective CVD (e.g. arthritis, weakness, rash, etc.) who are subsequently evaluated to assess for the presence of pulmonary disease.[3–6] In contrast, the existence of a new CVD diagnosis in those first presenting to a pulmonologist with symptoms of ILD, such as cough and dyspnea, remains largely unknown.

In the early 1970s, autoantibodies were first described in those with idiopathic pulmonary fibrosis (IPF)[7]; positive anti-nuclear antibodies (ANA) were demonstrated in nearly 50% of these patients.[7] However, the significance of the positive ANAs in this setting was unclear as many were of low titer. Notably, a recent publication hypothesized idiopathic non-specific interstitial pneumonitis (NSIP) to be an autoimmune disorder: the pulmonary manifestation of an undifferentiated connective tissue disease (UCTD).[8] Further, ILD can clearly be the presenting symptom of several CVDs.[9] However, the ability to identify previously unrecognized and undiagnosed CVD in patients presenting with ILD has not been systematically evaluated.

The ascertainment of CVD in association with ILD (CVD-ILD) in contrast to IPF alone is relevant both for prognostic and therapeutic purposes. Of note, NSIP, the lung histopathology most commonly associated with CVD-ILD,[10,11] confers a considerably better prognosis than usual interstitial pneumonitis (UIP), the histopathology associated with IPF.[12] Moreover, appreciation for the limited efficacy and known toxicities associated with immunosuppressive therapy for IPF is a relevant consideration in therapeutic recommendations.[13] Thus, it is critically important to differentiate CVD-ILD patients from those with IPF alone, inasmuch as the CVD-ILD population would be expected to experience a more favorable risk-benefit ratio from treatment.

We therefore sought to determine the frequency of previously undiagnosed CVD in a cohort of patients presenting to an ILD clinic. Further, we examined the association of several common and frequently used laboratory tests with the diagnosis of a new CVD.

Materials/patients and methods

Study subjects

This was a retrospective study of consecutive patients referred to the Johns Hopkins Interstitial Lung Disease Clinic and was approved by the Institutional Review Board. Medical records of all patients evaluated at the ILD Clinic from June 2000 to July 2006 were reviewed. Patients with prior diagnoses of sarcoidosis or systemic sclerosis were evaluated in separate subspecialty clinics. A diagnosis of ILD was made based on criteria including consistent clinical features and pulmonary function testing, radiographic evidence of interstitial disease, and/or lung histopathology consistent with this diagnosis.[14] All patients referred to our center with ILD had abnormal high resolution computed tomography scans of their lungs, scans which were re-reviewed at our center to confirm the presence of ILD. One hundred-sixty patients satisfied the criteria for ILD, the majority of whom were referred for cough or dyspnea. Among this group, 121 (76%) had at least one autoantibody assayed during their clinical evaluation. Seven of these patients were excluded from analysis when their pulmonary disorder was attributed to medication toxicity (rituximab ($n = 1$), amiodarone ($n = 2$)), to asbestos fiber exposure ($n = 1$), or attributed to sarcoidosis ($n = 3$). The remaining 114 patients had both radiographically or histologically confirmed ILD *and* at least one autoantibody (antinuclear antibody, anti-Ro, anti-La, anti-Scl 70 antibody, rheumatoid factor, or myositis-specific antibody) (Jo-1, anti-PL-7, anti-SRP, anti-Mi-2, anti-EJ, anti-OJ), or myositis-associated antibody (anti-Ku) assayed during their work-up and form the basis of this analysis.

Study design and methods

Demographic features were uniformly recorded, including age at presentation to the ILD clinic, first ILD-related symptom, and presence of muscle weakness on exam. Laboratory data included the above autoantibodies, as well as inflammatory markers (erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)) obtained within one month of presentation to the ILD clinic. In addition, available levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatine phosphokinase (CPK) and aldolase closest to presentation were recorded. Results of lung biopsies, muscle biopsies, and electromyogram (EMG/NCS) were recorded. Lung biopsies were performed during routine clinical evaluation in accordance with ATS /ERS guidelines for the evaluation of idiopathic interstitial pneumonias.[14] All available lung biopsies were reviewed by a lung pathologist at Johns Hopkins with expertise in ILD. Disease duration was defined as the period of time from the first ILD-related symptom to initial evaluation at the ILD clinic.

The American College of Rheumatology (ACR) criteria for rheumatoid arthritis (RA), systemic sclerosis (SSc), systemic lupus erythematosus (SLE), Wegener's granulomatosis (WG), primary Sjögren's syndrome (PSS), and Bohan and Peter's criteria for polymyositis (PM) and dermatomyositis (DM) were used to establish a diagnosis of a CVD.[15–20] After evaluation by a rheumatologist, patients with two or more signs and symptoms of a CVD (e.g. polyarthralgias/arthritis, sicca symptoms, Raynaud's phenomenon) and a positive ANA without fulfilling criteria for a well defined CVD were considered to have a UCTD.[21–23] In addition, an established CVD was defined as an existing diagnosis of CVD prior to presentation to the ILD Clinic. A new diagnosis of CVD was defined as a diagnosis which satisfied published criteria, and was established only after and as a result of evaluation at the ILD Clinic.

Analysis

Descriptive statistics including proportions, means and standard deviations were computed. The Shapiro–Wilk test was used to assess normality of the data. Univariate comparisons of patients with CVD-ILD to those without CVD were performed using unpaired *t*-tests for normally distributed variables or Fisher's exact test and Kruskall–Wallis tests for non-parametric variables.[24] A *p*-value ≤ 0.05 was considered significant. Analyses were performed with Stata Statistical Software release 9 (StataCorp, 2005, College Station, TX).

Results

The study population of 114 patients with ILD was comprised of 69% women and 69% Caucasians. Mean age at onset of symptoms was 58.8 ± 13.4 years; mean disease duration was 2.4 ± 3.2 years (Table 1). The vast majority reported having pulmonary symptoms or abnormal chest imaging as the presenting feature of ILD. Dyspnea (40%) and cough (25%) were the most common symptoms at presentation. Among patients presenting with non-pulmonary symptoms, 6 (5%) were noted to have subjective muscle weakness.

Overall, there were 34 patients who satisfied criteria for a well-defined CVD. These were equally divided into established and new diagnoses of a CVD. Thus, 17 (50%) patients presented with an established CVD, and an additional 17 patients were diagnosed with a new CVD diagnosis subsequent to and as a direct result of their evaluation at the ILD Clinic. The CVD subtype among the established CVD-ILD cases were as follows: 5 had idiopathic inflammatory myositis, 5 had RA, 3 had SLE, 2 had overlap syndrome, 1 had Sjogren's syndrome, and 1 had SSc. We performed univariate analyses of clinical characteristics between the new CVD-ILD group and the non-CVD-ILD group. Those with a new diagnosis of CVD were significantly younger than the 80 patients without a CVD; their mean age at presentation was 51 compared to 60 years, respectively ($p = 0.01$). There were no other significant differences in demographic or clinical features between the new CVD-ILD and the non-CVD-ILD groups.

During the clinical evaluation, 105 patients (92%) had two or more autoantibodies tested. Seventy-five (66%) of these patients were seropositive for at least one autoantibody whereas 26 patients (23%) had 2 or more positive autoantibodies. The most frequent positive autoantibody was an ANA ($n = 61$; 56% of patients tested) followed by rheumatoid factor ($n = 28$; 31% of patients tested), then anti-Ro ($n = 10$; 15% of patients tested), anti-Jo-1 ($n = 6$; 11% of patients tested), anti-Scl 70 ($n = 3$; 5% of patients tested), and anti-La ($n = 2$; 3% of patients tested). Six patients were evaluated for myositis-associated and myositis-specific antibodies (other than Jo-1); 2 of these patients had an anti-PL-7 antibody ($n = 2$; 33% of patients tested) and inflammatory myositis (Table 2). There was

Table 1 Clinical characteristics of ILD subjects with and without CVD.

Characteristics	CVD-ILD, $n = 34$		Non CVD-ILD, $n = 80$	*P*-value[a]
	Established, $n = 17$[b]	New, $n = 17$		
Age at presentation to ILD clinic, average years (range)	57.5 (26–84)	51.4 (30–79)	60.0 (26–85)	0.01
Race				1.0
Caucasian, not Hispanic, *n* (%)	9 (53)	12 (71)	58 (73)	
African-American, not Hispanic, *n* (%)	7 (41)	4 (23)	17 (21)	
Asian, *n* (%)	1 (6)	1 (6)	4 (5)	
Hispanic, *n* (%)	0 (0)	0 (0)	1 (1)	
Gender				1.0
Female, *n* (%)	15 (88)	11 (65)	53 (66)	
Male, *n* (%)	2 (12)	6 (35)	27 (34)	
Disease duration at presentation, average years (range)	1.51 (0.3–7.9)[b]	1.57 (0.3–5.3)[b]	2.8 (0.1–18.8)[b]	0.21
Reported symptom/sign at onset				0.99
Dyspnea, *n* (%)	6 (35)	8 (47)	32 (40)	
Cough, *n* (%)	2 (12)	3 (18)	23 (29)	
Pneumonia with or without infiltrate, *n* (%)	1 (6)	2 (12)	8 (10)	
URI/flu symptoms, *n* (%)	0 (0)	2 (12)	8 (10)	
Abnormal chest imaging, *n* (%)[c]	2 (12)	1 (6)	5 (6)	
Chest pain, *n* (%)	0 (0)	0 (0)	1 (1)	
Weakness, *n* (%)	5 (29)	0 (0)	1 (1)	
Other, *n* (%)	1 (6)	1 (6)	6 (8)	
Unknown, *n* (%)	1 (6)	0 (0)	2 (3)	

[a] Comparison between new CVD ($n = 17$) and non CVD-ILD subjects ($n = 80$).
[b] No significant differences were seen between patients with established CVD and those with a new CVD diagnosis by age at presentation, race, gender, disease duration, and symptoms at disease onset.
[c] These were asymptomatic patients, identified by an incidental finding on chest imaging, which was performed for purposes other than evaluation of ILD.

a range of titer levels among the patients with positive ANA results. In particular, of the 29 patients who had a positive ANA at a titer of $\geq$1:320, 18 (62%) had an underlying CVD ($p = 0.01$). In contrast, seropositivity for rheumatoid factor was not associated with the presence of a CVD diagnosis ($p = 1.0$).

We specifically examined the serologic profile of the patients with a new CVD diagnosis that followed from their evaluation at the ILD Clinic. Among these 17 patients, 12 had a positive ANA (71%). Though only 8 were seropositive for ANA at a titer of >1:320, this titer was only present in 11 of 34 patients without a CVD ($p = 0.049$). In addition, 4 (33%) of the patients with a new CVD diagnosis were seropositive for anti-Ro; none were seropositive for Scl70 or La antibody (Table 2). In contrast to the titer level, the pattern upon immunofluorescence staining did not distinguish those with a new CVD from those without CVD-ILD. The centromere pattern on ANA testing was not present in any patient.

Diagnostic markers of inflammation were measured in the majority of the study population (Table 3). Notably, the erythrocyte sedimentation rate (ESR), an acute phase reactant and non-specific marker of inflammation, was elevated in the majority of the patients in whom the test was performed. However, there was no significant difference in mean ESR value between patients with and without CVD. In contrast, markers of muscle inflammation, CPK and aldolase, were elevated in 26 of 93 (28%) patients with and 22 of 65 (34%) tested patients without a CVD diagnosis, respectively, during their clinical course. There was a significantly greater proportion of patients with a new CVD diagnosis who had elevations in CPK and aldolase compared with the non CVD-ILD group ($p < 0.001$ and $p = 0.001$, respectively). Thus, even though the median values for both CPK and aldolase were within the normal range in all groups, the proportion of patients with values exceeding the upper limit of normal did, in fact, distinguish the CVD from the non-CVD group ($p < 0.001$). There were no significant differences in median levels of ALT or AST between the new CVD compared with the non CVD-ILD group. Interestingly, 12 of the 26 (46%) patients with an elevated CPK and 10 of 22 (45%) patients with an elevated aldolase value were ultimately diagnosed with an inflammatory myositis.

Seventy-three patients had lung biopsies performed: 61 patients (84%) had surgical lung biopsies while 12 (16%) had transbronchial biopsies. The most common pathologic findings on surgical lung biopsy were UIP ($n = 20$) in 27% of patients and NSIP ($n = 18$) in 25% (Table 4). NSIP was the only lung histopathology significantly associated with CVD-ILD (new and established) ($p = .03$). There was a trend toward significance between histological pattern of NSIP and a new CVD diagnosis ($p = 0.07$). Of the 20 patients with histological evidence of UIP, 3 (15%) were diagnosed with a CVD compared with 9 out of 18 (50%) patients with NSIP (Table 4).

Although only 5 patients reported symptoms of weakness (Table 1), 21 patients (19%) were found to have objective

Table 2 Autoantibody profile of ILD subjects with and without CVD.[d]

Autoantibody	CVD-ILD, $n = 34$		Non CVD-ILD, $n = 80$	P-value[c]
	Established	New		
ANA	$N = 16$	$N = 17$	$N = 76$	
Positive, n (%)	15 (94)	12 (71)	34 (45)	0.07
ANA pattern[a]	$N = 19$	$N = 11$	$N = 32$	
Speckled, n (%)	9 (47)	5 (45)	21 (60)	0.3
Homogenous, n (%)	4 (21)	4 (36)	3 (9)	0.06
Nucleolar, n (%)	6 (32)	2 (18)	11 (31)	0.5
ANA titer	$N = 15$	$N = 12$[b]	$N = 34$	
$\geq$1:640, n (%)	10 (67)	7 (58)	7 (21)	0.03
1:320, n (%)	0 (0)	1 (8)	4 (12)	1.0
1:160, n (%)	3 (20)	1 (8)	8 (23)	0.4
1:80, n (%)	0 (0)	0 (0)	5 (15)	0.3
1:40, n (%)	2 (13)	3 (25)	10 (29)	1.0
Rheumatoid factor (Rf)	$N = 16$	$N = 12$	$N = 61$	
Positive, n (%)	8 (50)	3 (25)	17 (28)	1.0
Anti-Ro	$N = 16$	$N = 12$	$N = 37$	
Positive, n (%)	2 (12)	4 (33)	4 (11)	0.09
Anti-La	$N = 16$	$N = 12$	$N = 37$	
Positive, n (%)	2 (12)	0 (0)	0 (0)	NA
Anti-Scl 70	$N = 11$	$N = 11$	$N = 42$	
Positive, n (%)	2 (18)	0 (0)	1 (2)	1.0

NA, not applicable.

[a] Patients may have more than one pattern.

[b] Percentages do not add to 100% due to rounding.

[c] Comparison between new CVD and non CVD-ILD patients.

[d] Six patients had myositis-associated and myositis-specific (other than Jo-1) antibodies screened and 2 had anti-PL-7 antibodies and were diagnosed as having a new CVD. Another 53 patients had anti-Jo-1 antibodies evaluated; 6 were positive and were diagnosed as having a CVD (4 with a new CVD).

Table 3 Laboratory evaluation of ILD subjects with and without CVD at presentation to the ILD Clinic.

Laboratory test	CVD-ILD, $n = 34$		Non CVD-ILD, $n = 80$	P-value[a]
	Established	New		
CPK elevated	$N = 16$	$N = 14$	$N = 63$	<0.001
Elevated, n (%)	8 (50)	9 (64)	9 (14)	
Aldolase elevated	$N = 11$	$N = 14$	$N = 40$	0.001
Elevated, n (%)	4 (36)	10 (71)	8 (20)	
AST	$N = 16$	$N = 16$	$N = 70$	0.27
Median (range) U/L	24.0 (12–380)	29.5 (15–218)	21.0 (13–43)	
ALT	$N = 16$	$N = 16$	$N = 70$	0.08
Median (range) U/L	20 (11–383)	27 (11–161)	22.5 (5–46)	
ESR	$N = 5$	$N = 12$	$N = 41$	
Median (range) mm/h	67.0 (26–85)	29.5 (4–131)	29.0 (1–97)	0.3
ESR elevated	$N = 5$	$N = 12$	$N = 41$	0.8
Elevated ESR n (%)	4 (80)	7 (58)	21 (51)	

[a] Comparison between new CVD and non CVD-ILD subjects.

evidence of muscle weakness on initial examination; proximal weakness was more common than distal weakness. Histologic evaluation for myositis was quite sensitive, in that pathologic review was positive for inflammatory myositis in 6 of 8 patients who underwent a muscle biopsy. In addition, 22 patients had EMG/NCS performed, among whom 73% demonstrated either a myopathy or neuropathy.

In this study population of 114 consecutive patients referred to a tertiary ILD clinic, nearly one-third ($n = 34$) had an underlying CVD. The most frequently associated rheumatic disease was inflammatory myositis occurring in 17 patients or one-half of the CVD-ILD group. In addition, 8 patients had SLE (24%), 5 had (15%) RA, and 3 patients had SSc (9%) (Table 5). While 17 patients presented to the ILD clinic with a known CVD diagnosis, it is noteworthy that among the remaining 97 patients, followed for a median of 11 months (range 0 months–5.6 years), there were 17 new diagnoses of CVD. Among the new CVD diagnoses, there were 10 cases of myositis, 3 of SLE, 2 UCTD, 1 SSc, and 1 case of Wegener's granulomatosis (Table 5). The observation that these new rheumatologic diagnoses were made at a mean interval of 2.2 months (range 0–6 months) following the first ILD clinic visit, suggests that the phenotypic expression of pulmonary and non-pulmonary disease manifestations occurred in close temporal relationship. Interestingly, two patients were diagnosed with an overlap syndrome in that they satisfied published criteria for more than one CVD; there was one patient with SLE, SSc and myositis overlap and one patient with SLE and myositis overlap.

Discussion

Interstitial lung disease may evolve from an underlying CVD and result in substantial morbidity and mortality.[1] Whereas the prevalence of pulmonary fibrosis in patients with a known CVD has been previously determined by ascertainment for co-existent lung disease among patients presenting first to a rheumatologist,[3–6] we sought to determine the frequency and of new and established CVD diagnoses among a cohort referred to a pulmonologist for ILD. A recent editorial underscores the merit of this approach and highlights the potential for missing the diagnosis of CVD in patients presenting with ILD as the ''forme fruste'' of the CVD.[25] Moreover, the identification of CVD-ILD can have critical importance in therapeutic decision-making and, likely, has a meaningful impact upon prognosis as well.

We specifically examined the frequency of CVD in a retrospective cohort of 114 consecutive patients referred

Table 4 Surgical lung biopsy results of ILD subjects with and without CVD.

Pathology	CVD-ILD		Non CVD-ILD, $n = 53$	P-value[a]
	Established, $n = 6$[b]	New, $n = 14$		
UIP, n (%)	0 (0)	3 (21)	17 (32)	0.53
NSIP, n (%)	3 (50)	6 (43)	9 (17)	0.07
BOOP, n (%)	1 (17)	3 (21)	4 (7)	0.15
Fibrosis, not further characterized, n (%)	0 (0)	0 (0)	3 (6)	
Non-diagnostic, n (%)	1 (17)	0 (0)	8 (15)	
Other, n (%)	1 (17)	2 (14)	12 (23)	

UIP, usual interstitial pneumonitis; NSIP, nonspecific pneumonitis; BOOP, bronchiolitis organizing pneumonia. Other includes: DAD, diffuse alveolar damage; RB, respiratory bronchiolitis; LIP, lymphocytic interstitial pneumonitis; HP, hypersensitivity pneumonitis; non-NSIP/UIP.

[a] Comparison between new CVD and non CVD-ILD subjects.

[b] Percentages do not add to 100% due to rounding.

Table 5 Underlying rheumatologic diagnoses of CVD-ILD subjects by ACR criteria.

Diagnosis of rheumatic disease	Established CVD-ILD, $n = 17$[a]	New CVD-ILD, $n = 17$[a]
Systemic lupus erythematosus, *n* (%)	3 (18)	3 (18)
Idiopathic inflammatory myositis, *n* (%)	5 (29)	10 (59)
Sjogren's syndrome, *n* (%)	1 (6)	0 (0)
Systemic sclerosis, *n* (%)	1 (6)	1 (6)
Undifferentiated connective tissue disease, *n* (%)	0 (0)	2 (12)
Rheumatoid arthritis, *n* (%)	5 (29)	0 (0)
Overlap syndrome, *n* (%)	2 (12)	0 (0)
Wegener's granulomatosis, *n* (%)	0 (0)	1 (6)

[a] Percentages do not add to 100% due to rounding; 1 patient had lupus/myositis overlap and 1 patient had myositis, lupus, and scleroderma overlap.

to an ILD clinic at an academic tertiary care center. Notably, 17 (15%) patients in this cohort were diagnosed with a new CVD which satisfied published criteria, as a direct consequence of their evaluation at the ILD clinic. In addition, we found that two-thirds ($n = 75$) demonstrate at least one positive autoantibody. The most common autoantibodies were ANA and rheumatoid factor in 54% ($n = 61$) and 25% ($n = 28$), respectively. A number of clinical and demographic parameters were further related to the establishment of a new CVD diagnosis. This included younger mean age at presentation, elevated levels of the muscle enzymes, CPK and aldolase, and high titers of antinuclear antibody.

The overall frequency of CVD in our population, including both established and new cases, was 30%: twice that reported in the New Mexico ILD registry, where 13% of patients with ILD had CVD.[26] This higher prevalence may reflect the referral pattern at our tertiary care ILD clinic. The relatively higher representation of lupus and myositis among the new CVD diagnoses in our cohort may similarly reflect the composition of our referent population or practice patterns. Nevertheless, our findings emphasize that a full range of CVD diagnoses may be observed in patients referred to an ILD clinic. Our experience suggests that myositis may be under-recognized in the ILD population, as the levels of CK and aldolase are often not markedly elevated and amyopathic forms of myositis with isolated lung disease does exist. We also find that at least one quarter of those with myositis and ILD who demonstrate anti-synthetase antibodies do not express the Jo-1 autoantibody. Thus, lack of widely available clinical testing for alternative antisynthetase antibodies might result in the under-recognition of this syndrome.

Consistent with a number of prior studies, we find that NSIP is the most common lung histopathology associated with CVD.[9] Nevertheless, over half the patients with CVD demonstrated pulmonary histopathologic findings other than NSIP, including UIP in 15% of the patients with a CVD. This reinforces the notion that a biopsy showing UIP does not rule out the possibility of an associated CVD. A recent and an earlier study indicate that CVD-UIP has improved survival in comparison with IPF-UIP.[27,28]

Our findings need be interpreted in light of the retrospective study design. First, the decision to obtain a particular serologic parameter and the manner in which the history and examination were conducted may have been influenced by the individual patient's symptoms and the physician's practice pattern. Future study in this area ought to incorporate a predetermined protocol for ascertainment of exposures and outcomes applied uniformly to all patients. Second, there were 39 patients among this consecutive cohort of ILD referrals for whom no autoantibodies were tested. Exclusion of this quarter of the referent population due to missing data likely overestimated the prevalence of positive autoantibodies and the frequency of new CVD diagnosis in the remaining 114 patients who formed the basis for our analyses. However, the demographic profile of the omitted patients, including age and race, revealed no statistical differences from the study population, suggesting that the treating physician's decision to send autoantibodies was not overtly affected by demographic characteristics. On the other hand, as CVD is often a process in evolution, we would predict that a number of individuals who did not meet criteria for CVD at the point of evaluation might subsequently do so. As one such example, one of the non-CVD patients was seropositive for Scl-70, an autoantibody with specificity for scleroderma, but did not yet satisfy diagnostic criteria for that disorder. Moreover, since the diagnostic criteria for a CVD are used for research purposes, we may have missed CVD cases diagnosed on clinical grounds.

The accurate recognition of CVD has significant therapeutic and prognostic implication We, therefore, sought to determine what clinical characteristics and serologic assays used routinely in clinical practice might identify patients with an underlying and heretofore unrecognized CVD. We found that while patients with a new CVD diagnosis were younger at presentation, there were no other demographic features that significantly associated with the presence of CVD.

One of the striking findings related to CVD status was the frequency of high titer positive ANA: a high titer ANA was associated with a new CVD diagnosis. A homogeneous immunofluorescence ANA pattern was seemingly associated with established and new CVD diagnoses. In a separate study of 276 patients with systemic sclerosis, a homogeneous ANA pattern was associated with pulmonary fibrosis.[29] In the same report, a centromere ANA pattern was negatively related to pulmonary fibrosis.[29] Consistent with these observations, in our study we found no patients with a centromere pattern among the 61 patients with a positive ANA and ILD. In contrast to a different recent study,[30] we did not find that rheumatoid factor predicted CVD, which may reflect demographic differences; our population was more likely to be female and African-American.

Our findings suggest that patients presenting for an ILD consultation merit an evaluation for a previously unrecognized CVD, including a minimum screening for ANA, CPK, and aldolase. These diagnostic studies all demonstrated high specificity in our study population, indicating that when positive, there was a high probability of having a CVD. Notably, 15% of the patients in this retrospective cohort were

diagnosed with a new diagnosis of CVD as a direct consequence of their ILD evaluation. Prompt detection and early treatment of these patients may lead to improved outcomes.

Conflict of interest statement

All of the authors have declared no conflict of interest relevant to this manuscript.

Acknowledgements

We thank Drs Paul Hassoun, Landon King, Peter Terry, Fredrick Wigley and Robert Wise for their thoughtful discussions of the manuscript. This study was supported by the Robert Jeffs' Memorial Fund for Pulmonary Fibrosis.

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